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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
NGUYEN, DAVE TRONG

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/06/2002 14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/601,444	Chang
Examiner	**Art Unit**
Dave Nguyen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 6, 2002*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-70* is/are pending in the application.

4a) Of the above, claim(s) *1-12, 29, 30, 39, and 51* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *13-28, 31-38, 40-50, and 52-70* is/are rejected.

7) ☒ Claim(s) *38, 47-50, and 58-62* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Jan 4, 2001* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *7 and 13*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Applicant's election with traverse of group II claims, *e.g.,* claims 13-28, 31-37, 40, 41-50, 63-70, and of species of a tumor cell targeting ligand, a therapeutic nucleic acid, a liposome mean diameter of about 30 to 75 nm, and a ratio of 0.1 to 50 nM liposomes per 1.0 ug nucleic acid, in the response filed April 26, 2001 is acknowledged. Applicant's election with traverse of a species of a therapeutic agent, which encodes a protein, in the response filed August 26, 2002 is also acknowledged.

Applicant mainly traverses that the present claims have not been to be either independent, or distinct under the definitions of 35 USC 121, that the alleged separate inventions fall into separate classifications, have a separate status in the art, or would require different fields of search, and in fact they do not, and that the PCT standards were to apply to the present application, applicant's comments are found persuasive in part. This as-filed application is filed 35 USC 371 and thus, the restriction of record is properly done under 35 USC 371. Under both PCT standard and 35 USC 121, the restricted groups have to be shown to be independent and distinct, and to the extent that applicant 's response states that that should have been only two restricted Groups, *e.g.,* Group I claims, claims 1-12, 29, 30, 38, 39, 47-51, and 58-62, and Group II claims, claims 13-28, 31-37, 40-50, and 63-70, the response, page 5), applicant's response is found persuasive. In addition and upon a further consideration, claim 38 (which is also dependent from claim 31), claim 52, and claims dependent there from have been rejoined to the proposed Group II claims. Therefore, the restriction of record with respect to other groups has been withdrawn by the examiners, and is maintained and made final for the two proposed Groups as set forth in applicant's response. Applicant also traverses the species restriction by stating that all of the claims share substantial common structures. Applicant 's traversal is found persuasive only for folate and transferrin, however, the fact that the claimed species are dependent from a generic structure that may embrace all of the species does not preclude a species restriction of record, particularly since a search of the base claims that embrace one particular species of a targeting ligand, a ratio, and/or a particular nuclei acid does not necessarily overlap with that of another species of another targeting ligand, ratio, and/or therapeutic nucleic

acid. It is also noted that upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a). Also, should applicant continue to traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

In view of the reasons set forth in the immediately preceding paragraph, applicant's election of the newly proposed Group II claims is acceptable.

Claims 1-12, 29, 30, 38, 39, 51, and 58-62 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention.

Claims 38, 47-50 and 58-62 are objected because the claims are also presently embracing non-elected invention. Amendment of the claims so as to render the claims being dependent on only the base claims of the elected invention is suggested.

Elected claims 13-28, 31-38, 40-50, 52-70 directed to a liposomal complex of less than 100 nm comprising a cell targeting ligand, a liposome and a therapeutic agent, and methods of providing the therapeutic agent to a target cell, and a process specifically adapted for the manufacture of the products that are claimed in the elected claimed invention, are pending for examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-22, 24-28, 31-38, 40-50, 52-70 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

While the as-filed specification only provides sufficient written description of liposomal vector carrier having a mean diameter of less than about 100nm, wherein the vector carrier comprises a liposomal complex composed of a cell-targeting ligand bound to a cationic lipid, a therapeutic agent, and a neutral or helper lipid, the as-filed specification does not provide sufficient written description of a representative number of species of liposomal carrier having a mean diameter of less than about 100nm. The as-filed application does not provide any description of any embodiment that details specific structures of any other liposomal carrier, which structures are deemed essential for the practice of the claimed invention, particularly those liposomal carriers which must exhibit a mean diameter of less than about 100 nm. Thus, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or assays (page 11 of the specification) and/or any other unspecified structure containing unspecified liposomal compounds/plasmid DNA with size limitation that are only described by

functional language, wherein the detailed and common structure of the genera of the claimed compounds was not described; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structure(s) of component(s) that are linked structurally in order to exhibit the disclosed biological functions as contemplated by the as-filed specification. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. Claiming unspecified molecular structures of liposomal vector complexes comprising any therapeutic agent including plasmid DNA and any liposome, which are known in the prior art not to have a size of less than 100nm, and yet are required to have a diameter of less than 100 nm, without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure structure(s) of material(s) other than the liposomal vector carrier having a mean diameter of less than about 100nm, wherein the vector carrier comprises a liposomal complex composed of a cell-targeting ligand bound to a cationic lipid, a therapeutic agent, and a neutral or helper lipid, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification.

Thus, In view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 13-22, 24-28, 31-38, 40-50, 52-70 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

1/ A liposomal vector carrier having a mean diameter of less than about 100 nm, wherein the vector carrier comprises a liposomal complex composed of a cell-targeting ligand bound to a cationic lipid which is DOTAP/DOPE, DDAB/DOPE, a plasmid DNA encoding a wild type p53 tumor suppressor protein;

2/ A method of delivering a nucleic acid encoding a protein to a mammal, the method comprising administering the liposomal vector carrier of 1/ into the mammal;

3/ A method of ameliorate a tumor in a mammal, the method comprising administering to the mammal a liposomal vector carrier having a mean diameter of less than about 100 nm, wherein the vector carrier comprises a liposomal complex composed of a cell-targeting ligand bound to a cationic lipid which is DOTAP/DOPE, DDAB/DOPE, a plasmid DNA encoding a wild type p53 tumor suppressor protein, thereby ameliorating the tumor in the mammal,

does not reasonably provide enablement for any other claimed embodiment as broadly claimed in the presently pending claims.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Specifically, since the claimed invention is not supported by a sufficient written description (for possessing of a genus of liposomal carriers as claimed), particularly in view of the reasons set forth above, one skilled in the art would not known how to use and make the claimed invention so that it would operate as intended, *e.g.* functions as a delivery vector complex that must exhibit a mean diameter of less than about 100 nm to deliver any compound to a target cell as intended by the as-filed specification.

In addition the presently pending claims are not enabled for any cationic lipid/helper lipid/DNA complex other than DDAB/DOPE/plasmid DNA and DOTAP/DOPE/plasmid DNA.

While the specification provides sufficient guidance including working examples showing the making of the complexes composed of DDAB/DOPE/cell targeting ligand/plasmid DNA or DOTAP/DOPE/ cell targeting ligand/plasmid DNA, wherein the entire complex has a mean diameter of 30-100nm (average 50 nm, page 77 of the specification), the issue is then would a skilled artisan be able to reasonably extrapolate from the guidance to the making and use of any other cationic lipid/ligand/DNA complex/therapeutic agent, which must be reduced in size to the required limitation of less than 100 nm, as a result of the only manufacturing process disclosed in the as-filed specification, wherein the process mainly employs step of mixing and incubating any targeting ligand with any cationic lipid, neutral or helper lipid, and any theapeutic agent, *e.g.,* hydrophobic proteins, hydrophilic proteins, hydrophilic drugs, hydrophobic drugs, small molecular weight drugs, antibodies, for a time period of 10-15 minutes.,

However, the state of the prior art with respect to the making of compact cationic liposomes/plasmid DNA, let alone any other therapeutic agent such as oligo antisense molecules, as exemplified by Lee *et al.,* Critial Reviews in Therapeutic Drug Carrier Systesm, 14, 2:173-206, 1997, states:

> Because uncondensed plasmid DNA has a hydrodynamic diameter in the same range as liposomes (100 –200 nm, depending on the number of base pairs and the topology of the molecule), it is difficult to produce compact vector particles without efficient DNA condensation.

> Cationic liposomes expecially those composed of monovalent cationic lipids, cannot condense DNA efficiently. Formation of spaghetti-like structures during liposome/DNA complexation is usually accompanied by the generation of vectors of relatively large size with a tendency to aggregate (page 187, last paragraph).

The essential feature of the average diameter of the liposomal complexes being below 100 nm or the accentric structure is disclosed for DOTAP/DOPE/ligand/plasmid DNA and DDAB/DOPE/ligand/plasmid DNA, however, the as-filed specification does not provide sufficient guidance for a skilled artisan, without any undue experimentation, but only on the basis of applicant disclose, which relies only on general steps of mixing and incubating the liposomal components within some ratios parameters, to reasonably adjust the liposome/plasmid DNA dimensions in such narrow ranges (normal is 100 or more).

With respect to applicant's contemplation of claiming any method of gene therapy and/or the use of any liposomal carrier having the claimed diameter as a vector gene therapy, the state of the prior art with respect to non-viral gene therapy remains reasonably unpredictable at the time the invention was made.

More specifically, Lee *et al.* states:

> Because gene transfer efficiency is determined by a large number of factors, many of which are not well understood, it is difficult to predict the performance of a specific cationic liposome formulation based simply on the cationic lipid structure and/or the lipid composition. The gene transfer property of a vector is determined by 1) particle (DNA/lipid) size; 2) lipid composition; 3) lipid/DNA ratio; 4) formulation procedure; 5) DNA concentration; 6/ strength and tissue specificity of the promoter and enhancer elements; 7) for *in vitro* gene delivery, cell line, duration of transfection, cell confluency level, presence or absence of serum, etc; and 8? For *in vivo* deliveyr , route of adminstration (page 184);

More specifically as to applicant's intended use of the claimed vector for systemic and targeted gene therapy for treating any disease or disorder, Kao *et al.* (Cancer Gene Therapy, 3, 4:250-256, 1996) teaches:

> Targeting of cationic liposomes to specific cell surface epitopes appears to provide us with a means not only to achieve selective delivery of gene therapy to specific cells but also to increase the efficiency of transfection *in vitro.* However, with one or two notable exception, to date there are no successful examples of satisfactory transfection after systemic administration of liposoems, and no examples exist of successful transfections *in vivo* using targeted liposomal DNA systemically. Although we have achieved targeted delivery of liposomal anticancer drugs to tumors *in vivo*, using long-circulating sterically stabilized liposomes, cationic lipid-DNA complexes have short circulation half-lives. We expect that consider formulation development, directed at increasing the circulation times of the liposomal DNA, will be needed before targeted DNA delivery to cancer cells will be needed before targeted DNA delivery to cancer cells will be realized *in vivo* (page 255, column 2).

The specification also does not provide sufficient guidance and/or evidence so as to overcome the doubts expressed by the art of record. A simple inhibition of a tumor in a murine model wherein a particular formulation of DOTAP/DOPE/ligand/p53 expressing plasmid DNA or of DDAB/DOPE/ligand/p53 expressing plasmid does not appear to be correlated to any therapeutic effect by using any other therapeutic DNA, in cancer gene therapy in any cancer patient, let alone in any other gene therapy for treating any disease or disorder in any animal. Therefore, one skilled in the art then turns to the state of the prior art for guidance as to the state of the art of gene therapy of employing a cationic lipid/DNA complex. The state of the art of gene therapy by employing any vector including those of non-viral vectors such as cationic lipids remains unpredictable. For example, the state of the art exemplified by Verma *et al.* (Nature, Vol. 389, 18:239-242,

September 1997) states that "the Achilles heel of gene therapy is gene delivery", that "thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression", that gene delivery methods using non-viral vectors "suffer from poor efficiency of delivery and transient expression of the gene", and that "although there are reagents that increase the efficiency of delivery, transient expression of the transgene is a conceptual hurdle that needs to be addresses" (page 239, column 3, first paragraph). In addition, Anderson, Nature, Vol. 392:25-30, 1998, summarized the state of the art before 1998, and teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (page 30, column 1, last paragraph). Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basis understanding of how vectors should be constructed, what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma *et al.* indicate that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2).

More importantly and even with applicant's exemplified DOPE/DOTAP liposomes, Filion (International J. of Pharmaceutics, 162:159-170, 1996, states:

[t]The use of cationic liposomes to target DNA to the gastrointestinal tract is inappropriate. Cationic DOPE/DOTAP liposomes are extremely toxic to CD1 mice following the administration of a single dose, provoking a profound and lethal hypothermia.

> Complementary to our results, we have identified a range of adverse effects associated with the use of cationic lipids or cationic liposome (Table 2). This non-exhaustive list demonstrates very clearly that cationic liposomes must be used with caution for DNA (or drug) delivery. We believe

> that alternatives to cationic liposomes for DNA therapy should be considered in order to avoid these dose-limiting and often fatal adverse effect (page 169, column 1).
>
> These results, in addition to the observation that cationic liposomes are extremely toxic following oral administration, indicate that DOPE/cationic lipid liposomes are not appropriate for DNA (or drug) delivery (abstract).

As such, there has been no evidentiary support from the as-filed application to show that on the basis of application's disclosure a skilled artisan would have been able to make and use the claimed cationic lipid/ligand/therapeutic liposomal complex in the context of any therapy including cancer therapy and/or cancer gene therapy. There is no evidence presented to show that the nexus from applicant's guidance and/or working examples to the subject matter as broadly claimed has been established.

Thus on basis of the *Wands* factors, it is not apparent how one skilled in the art determines, without undue experimentation, which of the disclosed DNA complexes generate a therapeutic effect in any and/or all gene therapy methods, nor is it apparent as to how one skilled in the art reasonably extrapolates from the disclosure of the as-filed specification to any and/or all *in vivo* delivery and/or expression methods wherein the only intended use of the methods is to generate a therapeutically intended effect, particularly given the lack of guidance and/or written support from the as-filed specification, the unpredictability of gene therapy, the lack of correlatble working examples, and/or the doubts expressed in the art of record.

Note that even while one of applicant's cationic lipid/biologically active molecule complex exhibits an inhibition effect on the growth of a tumor in a nude mouse, the court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

> It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use

the invention as broadly as it is claimed.
In re Vaeck, 947 F.2d 488, 496 & n.23. 30 USPQ2d 1438, 1445 & n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specifications provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [footnote omitted].

On this record, it is apparent that applicant's amended subject matter, without any proper written support and sufficient guidance from the as-filed specification, provides no more than a plan or invitation for those skill in the art to further unduly experiment with any cationic lipid/biologically active molecule complex so as to provide any therapy effect in any animal.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in—

(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or

(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 13, 16, 17, 19-21, 24-25 are rejected under 35 USC 102(b) as being anticipated by Wang *et*

al. (Biochemistry, Vol. 92:3318-3312, 1995).

Wang teaches an liposomal carrier composed folate-PEG –distearoylphophatidylethanolamine, which encapsulates antidesne oligos against the epidermal growth factor (EGF) receptor in cancer KB cells (entire document). Wang further teaches on page 3318, column 2 that "folate has already been exploited to nondestructively deliver antibodies, toxinds, enzymes, small organic molecules, genes, and liposomes into-receptor bearing cells", and that "folate-PEG-liposomes can deliver sufficient antisense against the growth factor receptor (EGFR) into KB cells to eliminate EGFR expression, to alter cell morphology, and to halt cell growth". On page 3319, column 2, Wang *et al.* teaches that the liposomal complexes can be formulated by a size reduction procedure of extrusion through a 100 nm polycarbonate membrane. As a result, the mean diameter of the liposomes after extrusion must necessarily be less than 100 nm. With respect to the ratio limitation, Wang *et al.* teaches a ratio of 2 nm the liposomes per 1 ug of antisense oligonucleotides on page 3319.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned

at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 13-17, 19-20, 22-28, 31, 33-38, 40-48, 63-70 are rejected under 35 USC 102(e) as being anticipated by, or in the alternative, under 35 USC 103(a) as being unpatentable over Cheng (US Pat NO. 6,077,834), as evidenced by page 76 and 77 of the as-filed specification.

Cheng teaches an identical claimed liposomal complex as claimed in the invention. The liposomal vector carrier of Cheng consists essentially of a liposomal complex composed of a cell-targeting ligand bound to a cationic lipid, a therapeutic nucleic acid encoding a therapeutic protein, and a neutral or helper lipid, *e.g.,* see columns, 7, 8, 11, and 18-20. Cationic lipids including DOTAP and DDAB, and neutral or helper lipids are disclosed on column 3. Receptor ligands including transferrin are also disclosed on column 3. On column 11, Cheng employs routine and/or standard amount of liposomes and DNA, *e.g.,* 3 uL of cationic lipids and 1.5 ug of plasmid DNA. For example, The transfection solution in Cheng (column 17) contains 3 ug of lipofectin, 16 ug of transferrin, and 1.5 ug of DNA. Table 4 also listed other exemplified amounts of liposomes such as 32 ug, 3ug, 4.2 ug and 4nM. More importantly, Cheng the claimed production process as claimed in claims 63-70 in the issued claims 1-17, wherein mixing and incubation are required before and/or after an addition of one of the essential component. Incubation time of 15 min is disclosed on column 11, line 5. Since the production process of Cheng is embraced by the claimed process of the examined claims, it would necessarily flow from the teaching of Cheng that the cationic lipid/transferrin/DNA complexes after mixing and incubation must exhibit a mean diameter of less than 100 nm or of 50 nm, particularly since the as-filed specification states on pages 76 and 77 as a result of

incubation and mixing (5-15 minutes, for example) of the liposomal complexes in the presence of transferring or other ligands in the mixture, a transition to an inverted hexagonal (HII) phase occurs that leads to an accentric onion-like core structure. As such, Cheng teaches both the steps of mixing and incubation as being required for the success of the delivery methods, Cheng inherently teaches the size and shape limitation of the liposomal complexes, particularly in the absence of evidence to the contrary. To the extent that other particular embodiments including specific ratio of lipids and DNA, the simultaneous shaking and incubation, such would have been minor modifications which do not contribute and unexpected result, and thus, would have been obvious for a skilled artisan to have employed as a matter of design choice. One of ordinary skill in the art would have been motivated to do because Cheng teaches that as long as a mixing (which is equivalent or embraced by the shaking or rocking term) and incubation a cell targeting ligand with cationic liposomal complexes is employed in combination with any known techniques of making a cationic lipid/DNA complexes, the delivery of any polynucleotide to a mammal can be achieved with a reasonable expectation of success.

Thus, the claimed invention as a whole is anticipatory, or in the alternative, was *prima facie* obvious.

Claims 13-17, 19-20, 22-28, 31, 33-38, 40-48, 63-70 are rejected under 35 USC 102(b) as being anticipated by, or in the alternative, under 35 USC 103(a) as being unpatentable over Cheng (Human Gene Therapy, Vol. 7: 275-282, 1996), as evidenced by page 76 and 77 of the as-filed specification.

Cheng teaches an identical claimed liposomal complex as claimed in the invention. The liposomal vector carrier of Cheng consists essentially of a liposomal complex composed of a cell-targeting ligand bound to a cationic lipid, a therapeutic nucleic acid encoding a therapeutic protein, and a neutral or helper lipid, *e.g.,* see columns, 7, 8, 11, and 18-20. Cationic lipids including lifofectin, lipofectACE, LipofectAMINE, and DC-Cholesterol, and neutral or helper lipids are disclosed in Table 4, . Receptor ligand transferrin is

disclosed throughout the reference. On page 276, column 2, Cheng employs routine and/or standard amount of liposomes and DNA, *e.g.,* 3 uL of cationic lipids and 1.5 ug of plasmid DNA. For example, The transfection solution in Cheng (page 276) contains 3 ug of lipofectin, 32 ug of transferrin, and 1.5 ug of DNA. More importantly, Cheng the claimed production process as claimed in claims 63-70 in the issued claims 1-17, wherein mixing and incubation are required before and/or after an addition of one of the essential component. Incubation time of 15 min is disclosed on page 276, column 1. Since the production process of Cheng is embraced by the claimed process of the examined claims, it would necessarily flow from the teaching of Cheng that the cationic lipid/transferrin/DNA complexes after mixing and incubation must exhibit a mean diameter of less than 100 nm or of 50 nm, particularly since the as-filed specification states on pages 76 and 77 as a result of incubation and mixing (5-15 minutes, for example) of the liposomal complexes in the presence of transferring or other ligands in the mixture, a transition to an inverted hexagonal (HII) phase occurs that leads to an accentric onion-like core structure. As such, Cheng teaches both the steps of mixing and incubation as being required for the success of the delivery methods, Cheng inherently teaches the size and shape limitation of the liposomal complexes, particularly in the absence of evidence to the contrary. To the extent that other particular embodiments including specific ratio of lipids and DNA, the simultaneous shaking (or rocking) and incubation, such would have been minor modifications which do not contribute and unexpected result, and thus, would have been obvious for a skilled artisan to have employed as a matter of design choice. One of ordinary skill in the art would have been motivated to do because Cheng teaches that as long as a gentle mixing (which is equivalent or embraced by the shaking or rocking term) and incubation a cell targeting ligand with cationic liposomal complexes is employed in combination with any known techniques of making a cationic lipid/DNA complexes, an enhanced delivery of any polynucleotide to a mammal as compared to other complexes without the presence of a targeting ligand non-covalently bound to the surface of the liposomal carrier can be achieved with a reasonable expectation of success.

Thus, the claimed invention as a whole is anticipatory, or in the alternative, was *prima facie* obvious.

Claims 13-17, 19-21, 23-28, 31, 33-38, 40-48, 63-70 are rejected under 35 USC 103(a) as being unpatentable over Cheng (US Pat NO. 6,077,834), as evidenced by page 76 and 77 of the as-filed specification, taken with Lee *et al.* (J. of Biological Chemistry, Vol. 271, No. 14, pp. 8481-8487, 1996) and Gao *et al.* (Biochemistry, 35: 1027-1036, 1996), and further in view of Unger, US Pat No. 6,028,066.

To the extent that Cheng does not disclose or teach an incorporation of polylysine or cationic species to a plasmid DNA before the step of mixing a targeting ligand to the condensed polylysine-DNA, which condensation even further reduces the size of the entire liposomal complex to 74 nm ± 14 nm, Lee *et al.* teach such incorporation and further teach the use of a folate bound liposomal carrier to deliver the condensed DNA to a receptor bearing tumor cell (entire disclosure, abstract).

In addition, Gao *et al* further teach advantages of employing polycation so as to potentiate cationic liposome-mediated delivery of any DNA to a cell in a mammal (entire disclosure). Ratios of liposome (3-10 nm) to 1 ug are exemplified on page 1032. Sizes of the entire particles of less than 100 nm are also disclosed on page 1033 bridging page 1044.

It would have been obvious for one of ordinary skill in the art to have employed polylysine to potentiate a cationic liposome-mediated delivery of any DNA to a cell in a mammal, such as the liposomal/targeting ligand/DNA complexes disclosed in the primary references. One would have been motivated to do so because Lee and Gao both teach that polylysine helps to potentiate cationic liposome-mediated delivery of any DNA to a cell in a mammal. One of ordinary skill in the art would also have been motivated to employ a folate as a targeting ligand. One would have been motivated to so because Lee teaches that folate-conjugated macromolecules and liposomes have been shown to be specifically taken up by cultured receptor bearing tumor cells (page 8481, column 2).

Note that it is also would have been obvious for one of ordinary skill in the art to have employed a

shaker or shaking techniques, in the preparation of liposomal formulation of the combined cited references. One of ordinary skill in the art would have been motivated to do so because Unger, one of many exemplified references, teaches that it is well known in the prior art of making lipid containing formulations to employ shaking techniques and/or vortexing to make or formulate liposomal vesicles containing stabilizing materials at a preferred size range (column 66, last paragraph, entire columns 67 and 68).

Thus, the claimed invention as a whole was *prima facie* obvious.

Claims 13-28, 31-38, 40-50, 52-70 are rejected under 35 USC 103(a) as being unpatentable over either US Pat NO. 6,077,834 (Cheng) or Cheng (Human Gene Therapy, Vol. 7: 275-282), taken with Roth (US Pat No. 6,069,134) and Wang et al. (Biochemistry, Vol. 92:3318-3312, 1995).

The '834 patent or Cheng is applied here as indicated above. The'834 patent and Cheng do not teach a combination method of killing tumor cells employing a combination of radiation or chemotherapy and a systemic administration of any vector carrier encoding a wild type p53 protein to a tumor bearing subject, nor the references teach that a cell targeting ligand is folate.

However, at the time the invention was made, Roth teaches a combination method of killing tumor cells employing a combination of radiation or chemotherapy and a systemic administration of any vector carrier encoding a wild type p53 protein to a tumor bearing subject, wherein the vector carrier includes a liposomal vector carrier (column 8, lines 42-62, column 21, column 38, claim 44).

In addition, Wang teaches on page 3318, column 2 that "folate has already been exploited to nondestructively deliver antibodies, toxinds, enzymes, small organic molecules, genes, and liposomes into-receptor bearing cells", and that "folate-PEG-liposomes can deliver sufficient antisense against the growth factor receptor (EGFR) into KB cells to eliminate EGFR expression, to alter cell morphology, and to halt cell growth".

It would have been obvious for one of ordinary skill in the art to have employed the delivery method and/or delivery vector carrier as disclosed in the primary references in the Roth reference. One of ordinary skill in the art would have been motivated to do so because Roth teaches that any known vector including a liposomal vector carrier can be used to express therapeutic p53 and because both primary references teach that liposomal vector carriers composed of a cell-targeting ligand bound to a cationic lipid, a therapeutic nucleic acid encoding a therapeutic protein, and a neutral or helper lipid are effective to enhance a targeted delivery of a therapeutic DNA to a cell in a mammal.

One of ordinary skill in the art would also have been motivated to employ folate as the cell targeting ligand in the liposomal vector and/or delivery methods as disclosed in the primary references taken with Roth. One would have been motivated to do so because Wang teaches on page 3318, column 2 that "folate has already been exploited to nondestructively deliver antibodies, toxinds, enzymes, small organic molecules, genes, and liposomes into-receptor bearing cells", and that "folate-PEG-liposomes can deliver sufficient antisense against the growth factor receptor (EGFR) into KB cells to eliminate EGFR expression, to alter cell morphology, and to halt cell growth".

Thus, the claimed invention as a whole was *prima facie* obvious.

Claims 13-28, 31-38, 40-50, 52-70 are rejected under 35 USC 103(a) as being unpatentable over either US Pat NO. 6,077,834 (Cheng) taken with Lee, Gao, and Unger, and further in view of Roth (US Pat No. 6,069,134).

The '834 patent taken with Lee, Gao, and Unger, are applied here as indicated above. The '834 patent taken with Lee, Gao and Unger does not teach a combination method of killing tumor cells employing a combination of radiation or chemotherapy and a systemic administration of any vector carrier encoding a wild type p53 protein to a tumor bearing subject.

However, at the time the invention was made, Roth teaches a combination method of killing tumor

cells employing a combination of radiation or chemotherapy and a systemic administration of any vector carrier encoding a wild type p53 protein to a tumor bearing subject, wherein the vector carrier includes a liposomal vector carrier (column 8, lines 42-62, column 21, column 38, claim 44).

It would have been obvious for one of ordinary skill in the art to have employed the delivery method and/or delivery vector carrier as disclosed in the '834 patent taken with Lee, Gao and Unger in the Roth reference. One of ordinary skill in the art would have been motivated to do so because Roth teaches that any known vector including a liposomal vector carrier can be used to express therapeutic p53 and because the '834 patent taken with Lee, Gao and Unger teaches that liposomal vector carriers composed of a cell-targeting ligand bound to a cationic lipid, a polylysine/condensed therapeutic nucleic acid encoding a therapeutic protein, and a neutral or helper lipid are effective to enhance a targeted delivery of a therapeutic DNA to a cell in a mammal.

One of ordinary skill in the art would also have been motivated to employ folate as the cell targeting ligand in the liposomal vector and/or delivery methods as disclosed in the primary references taken with Roth. One would have been motivated to do so because Wang teaches on page 3318, column 2 that "folate has already been exploited to nondestructively deliver antibodies, toxinds, enzymes, small organic molecules, genes, and liposomes into-receptor bearing cells", and that "folate-PEG-liposomes can deliver sufficient antisense against the growth factor receptor (EGFR) into KB cells to eliminate EGFR expression, to alter cell morphology, and to halt cell growth".

Thus, the claimed invention as a whole was *prima facie* obvious.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst Dianiece Jacobs, whose telephone number is **(703) 305-3388.**

Any inquiry concerning this communication or earlier communications from the

examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
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DAVE T. NGUYEN
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